BEFORE THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Bernd RIEDL et al.		Confirmation No.:	9631
Serial No.:	10/071,248	Examiner:	Rita J. Desai
Filed:	February 11, 2002	Group Art Unit:	1625

Title: METHOD AND/OR PROCESS FOR PREPARING ω-CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on September 25, 2006, herewith is Appellants' Brief on Appeal. The enclosed check includes the statutory fee of $500.00 as set forth under § 41.20(b)(2) and the fee for two month extension of time. This is an appeal from the final rejection of May 25, 2006.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is: BAYER PHARMACEUTICALS CORPORATION, 400 Morgan Lane, West Haven, Connecticut 06516, United States of America, a corporation organized under the laws of the State of Delaware, United States of America.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to: Commissioner of Patents, P O Box 1450, Alexandria, VA 22313-1450 on: January 25, 2007

Name: Richard J. Travers

Signature: [signature]

(ii) RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to Appellant or Appellant's legal representative which are related to this appeal or will be directly affected by or have any bearing on the Board's decision in the pending appeal.

(iii) STATUS OF CLAIMS

Claims 1-15 and 22 are pending in the present application.

Claims 1-15 and 22 are rejected. All rejected claims are on appeal.

(iv) STATUS OF AMENDMENTS

No amendments were filed after final.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

The claims on appeal are directed to compounds according to formulae Ia, which are aryl urea compounds which inhibit the raf pathway (see page 2, lines 17-18) and the p38 pathway (see page 97, lines 6-16), and methods of treating or preventing osteoporosis and inflammation with compounds of formula Ia (see p38 assay on page 97, lines 6-16).

The compounds of formula Ia are claimed in independent claim 1. Support for the compounds of claim 1 can be found, for example, in the broad generic disclosure that appears on page 2, line 22 to page 6, line 8 and the specific disclosure that appears on page 6 , lines 9-22.

Dependent claims 2-9 define subgeneric groups of compounds within the scope of formula Ia of claim 1. Support for these claims is found within the description of formula Ia on page 6 , line 22.

Dependent claims 10-13 define specific compounds within the scope of formula Ia of claim 1. Support for these claims is found on page 7, lines 20-25.

Independent claim 14 defines compounds of formula Ib. The compounds of formula Ib are a subgenus of compounds of formula Ia defined in independent claim 1. Support for the compounds of formula Ib is found on page 6, line 24, to page 7, line 5.

Independent claim 15 defines compounds of formula Ic. The compounds of formula Ic are a subgenus of compounds of formula Ia defined in independent claim 1. Support for the compounds of formula Ic is found on page 7, lines 6-16.

The methods for treating or preventing osteoporosis and inflammation with compounds of formula Ia are claimed in claim 22. Support for this claim can be found, for example, on page 97, lines 6-16, which describes a p38 assay for testing the compounds disclosed for activity known to have a nexus with the treatment of various diseases including osteoporosis and inflammation. Support is also found on page 98, line 1, which discloses the results obtained from the p38 assay for certain exemplified compounds structurally similar to those claimed.

(vi) GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The sole ground for rejection is under 35 U.S.C. § 112, first paragraph, and is as to whether the specification provides an enabling disclosure for the compounds of claims 1-15 and methods of treating or preventing osteoporosis and inflammation of claim 22.

(vii) ARGUMENT

- The rejection under 35 U.S.C. § 112, first paragraph, as to whether the specification provides an enabling disclosure for the compounds of claims 1-15 and methods of treating or preventing osteoporosis and inflammation of claim 22.

Claims 1-15

Appellants submit that there is no basis for the rejection of claims 1-15 under 35 USC § 112, first paragraph, and that one skilled in the art could make and use the compounds defined therein based on the disclosure within the specification.

The compounds of claims 1-15 are clearly defined in the specification on page 6, line 9, through page 7, line 16. No evidence has been presented or allegations made that the compounds claimed are not clearly defined. With the structure of the claimed compounds clearly defined by formula Ia, one of ordinary skill in art could synthesize these compounds without undue experimentation relying only on conventional methods for synthesizing ureas known in the art. A representative prior art disclosure of methods for synthesizing ureas is WO 98/52558, published November 26, 1998.

In addition to the conventional methods, the specification provides ample guidance to one skilled in the art as to how to prepare the claimed compounds. General preparative methods for synthesizing ureas are given on pages 15-17. One skilled in the art would recognize the appropriate starting materials (substituted anilines and substituted nitro-aryls) necessary to employ in these methods to arrive at the claimed compounds. Methods for preparing the starting materials are well known (substituted anilines and substituted nitro-aryls) and publications, which describe such methods, are disclosed on page 15 of the specification and incorporated by reference. Additional guidance on the selection of starting materials and reaction conditions is provided by the general synthesis procedures provided on pages 26-62 and further guidance is provided by the specific examples described on pages 62-97. These specific examples include compounds having the cyclic structures of formula Ia but not the required -OH or -$OC(O)C_1$-C_4 alkyl substituents of the claimed compounds. Syntheses that prepare ureas having corresponding methoxy substituents and halogen substituents are also illustrated. Based on the disclosure within the specification and conventional methods known in the art, one of ordinary skill in the art clearly would be able to prepare the claimed compounds without undue experimentation. No evidence has been presented to the contrary.

As to using the compounds of claims 1-15, the specification clearly discloses that the compounds have pharmacological activity based on the disclosure on page 2, lines 5-15; page 9. line 15, to page 14, line 24; and assays disclosed on pages 97-100. The compounds are said to be effective in treating tumors and/or cancerous cell growth on page 2, line 8 and hyperproliferative disorders on page 9, line 15. Specific cancers(e.g., carcinomas, myeloid disorders and adenomas) are disclosed on page 2, lines 14-15 and others are described on page 10, line 14, to page 11, line 30. Structurally related compounds (those which do not have the required -OH or -$OC(O)C_1$-C_4 alkyl substituents) are shown to be effective in inhibiting raf and p38. It is recognized in the art that inhibition of raf kinase is correlated with the inhibition of growth of a variety of human tumor types, as discussed in citations mentioned in the specification on page 1, line 32 to page 2, line 2. It is also recognized in the art that inhibitors of p38 will be effective in treating osteoporosis and inflammation, See WO 98/52558, page 2,. lines 19 and 21; and page 7, lines 9 and 21. This published application teaches on page 2, lines 11-14, "Inhibition of p38 has been shown to inhibit both cytokine production (e.g., TNFα, IL-1, IL-6, IL-8) and

proteolytic enzyme production (e.g., MMP-1, MMP-3) *in vitro* and/or *in vivo*." This published application also cites a large volume of prior art that provides the nexus between, for example, TNFα and various diseases, including, "a wide variety of inflammatory and/or immunomodulatory diseases" such as "postmenopausal osteoporosis."

No evidence has been presented or allegations made that the disclosed utility of the claimed compounds as pharmaceuticals is unclear.

The specification provides ample guidance on how to use the claimed compounds in treating these various conditions. Disclosure is provided on how to prepare pharmaceutical compositions with the compounds of this invention, including dosage ranges, and how to administer these compositions in the treatment of various conditions. See, e.g., pages 9-15. The specification also provides assays for determining the activity levels of the compounds on pages 97-100. One of ordinary skill in the art by performing the same assays described in the specification or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating the various conditions known in the art to be correlated with raf inhibition and p38 inhibition. This is absolutely routine in the field.

"T[t]he [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Given the extent of the disclosure provided, it would at most involve routine experimentation, if any at all, for one of ordinary skill in the art to make and use the compounds of claims 1-15 in treating various conditions such as cancer and other hyperproliferative disorders, osteoporosis and inflammation.

Even absent the specification disclosures discussed above, the rejection of Claims 1-15 is clearly deficient in general under controlling case law. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance

with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made regarding the guidance provided with respect to the treatment of osteoporosis and inflammation. No mention is made of the other claimed utilities in treating cancer and other hyperproliferative disorders and no evidence has been presented that the disclosure is insufficient for any claimed utility. In the absence of such evidence, Appellants submit the rejection of claims 1-15 under 35 U.S.C. § 112, first paragraph, should be reversed.

Claim 22

First and foremost, there is no indication that one of ordinary skill in the art would have questioned whether the claimed compounds of formula Ia would be effective in treating osteoporosis and inflammation as defined in claim 22, so there is no basis for the rejection of this claim under 35 USC § 112, first paragraph. See Rasmusson v. Smithkline Beecham Co., 75 USPQ2d 1297 (CA FC 2005). Thus, the enablement rejection is improper. As discussed above, it is incumbent upon the Patent and Trademark Office to provide reasons as to why enablement is insufficient (See M.P.E.P 2164.04). The PTO has not presented any evidence or reason to doubt that the compounds of formula Ia can be used to treat osteoporosis and inflammation consistent with the teachings within the disclosure, see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). Only the general allegation that "the specification provides no guidance to treat inflammation and osteoporosis," has been made.

Appellants submit that one skilled in the art could perform the methods defined in claim 22 based on the disclosure within the specification and what was known in the art at the time of filing the application, particularly in view of the disclosure of p38 inhibition by structurally related compounds.

As discussed above, the specification clearly provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of claims 1-15, including dosage ranges, and how to administer these pharmaceutical compositions. The specification also provides disclosure that structurally related compounds inhibit p38. Because some of these structurally related compounds vary from those of formula Ia only in the required OH or $-OC(O)C_1$-C_4 alkyl substituents, while varying

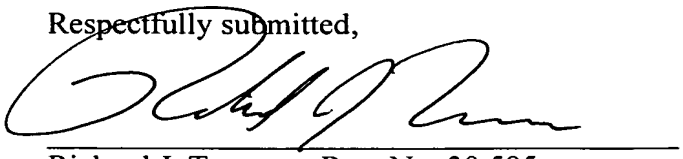
significantly from each other, it is not objectively doubtable that the compounds of formula Ia also inhibit p38 in a manner consistent with the exemplified compounds.

If the p38 activity of the compounds of formula Ia is not objectively doubtable, their utility in the methods of claim 22 can not be objectively doubtable. Given this disclosure within the specification and the nexus between p38 inhibitors and the treatment of osteoporosis and inflammation known in the art, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat osteoporosis or inflammation with a compound of formula Ia. "[T]he [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Even a considerable amount of experimentation is permissible, if it is merely routine.

There is no requirement that applicant exemplify the method of claim 22 in a working example or dedicated assay to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *In re Howarth*, 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); and *In re Gay*, 309 F.2d 769, 774, 135 U.S.P.Q 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.") Instead, there is no requirement for any examples. See, for example, *Marzocchi*, supra, stating that how "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

For the reasons indicated above, Appellants submit that the subject matter of claims 1-15 and 22 is sufficiently enabled to meet the requirements of 35 U.S.C.§ 112, first paragraph and that this rejection should be reversed.

Respectfully submitted,



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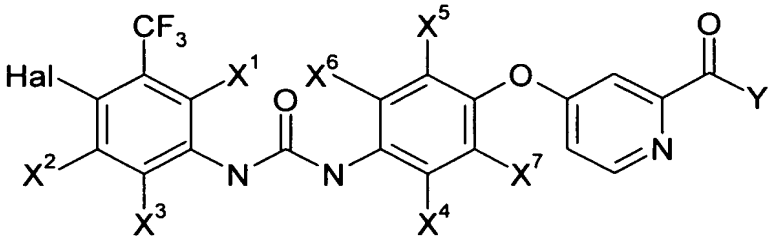
Attorney Docket No.: **BAYER-0015-P04**

Date: **January 25, 2007**

(viii) CLAIMS APPENDIX

1. A compound of formula (Ia)



(Ia)

wherein,

Y is NHR,

Hal is chlorine or bromine,

R is H, CH_3 or CH_2OH, and

X^1 to X^7 are each, independently, H, OH or -OC(O)C_1-C_4 alkyl,

or a salt or purified stereoisomer thereof,

with the proviso that at least one of X^1 to X^7 is OH or -OC(O)C_1-C_4 alkyl.

2. A compound of claim 1 wherein X^1 is OH or -OC(O)C_1-C_4 alkyl.

3. A compound of claim 1 wherein X^2 is OH or -OC(O)C_1-C_4 alkyl.

4. A compound of claim 1 wherein X^3 is OH or -OC(O)C_1-C_4 alkyl.

5. A compound of claim 1 wherein X^4 is OH or -OC(O)C_1-C_4 alkyl.

6. A compound of claim 1 wherein X^5 is OH or -OC(O)C_1-C_4 alkyl.

7. A compound of claim 1 wherein X^6 is OH or -OC(O)C_1-C_4 alkyl.

8. A compound of claim 1 wherein X^7 is OH or -OC(O)C_1-C_4 alkyl.

9. A compound of claim 1 wherein Hal is chlorine.

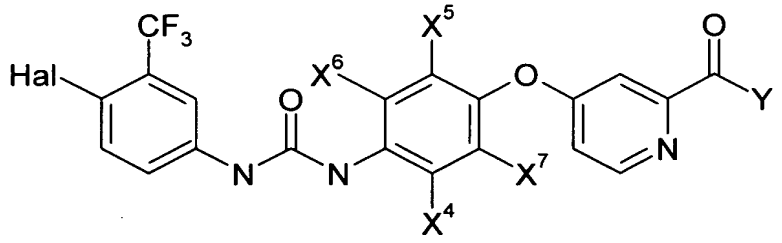
10. A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]2-(hydroxy)phenoxy}-2-pyridine carboxamide.

11. A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]3-(hydroxy)phenoxy}-2-pyridine carboxamide.

12. A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]5-(hydroxy)phenoxy}-2-pyridine carboxamide.

13. A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]6-(hydroxy)phenoxy}-2-pyridine carboxamide.

14. A compound of formula (Ib)



(Ib)

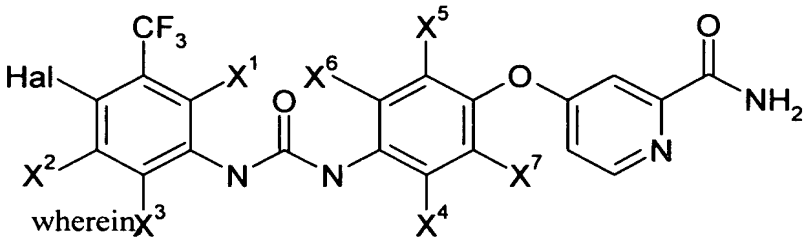
wherein,

Y	is NHR,
Hal	is chlorine or bromine,
R	is H, CH_3 or CH_2OH, and
X^4 to X^7	are each, independently, H, OH or -OC(O)C_1-C_4 alkyl,

or a salt or purified stereoisomer thereof,

with the proviso that at least one of X^4 to X^7 is OH or -OC(O)C_1-C_4 alkyl.

15. A compound of formula (Ic)



(Ic)

Hal is chlorine or bromine, and

X^1 to X^7 are each, independently, H, OH or -OC(O)C_1-C_4 alkyl,

or a salt or purified stereoisomer thereof,

with the proviso that at least one of X^1 to X^7 is OH or -OC(O)C_1-C_4 alkyl.

22. A method of treating osteoporosis and inflammation, in a mammal by administering an effective amount of a compound of claim 1.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None